One of the first and most popular examples of historical diagnosis is provided by an examination of King George III and the records of his significant illness. Plagued with acute attacks of intense abdominal pain, curiously-coloured urine, and a constellation of neuropsychiatric symptoms, historians were at a loss for an explanation for nearly two centuries. It is now generally accepted that King George suffered from some form of porphyria, likely acute intermittent porphyria (AIP) or variegate porphyria (VP). Porphyria diseases are at their root a variety of disorders of heme synthesis. Symptoms are believed to result from the accumulation of biosynthetic intermediates. It is the intent of this paper to outline AIP and VP and their association with many influential people from the past. Maintaining a high index of suspicion for these entities you will not only undoubtedly impress your senior resident – you may also find yourself in royal company for your efforts.

Introduction

One cannot discuss the history of rare diseases without mention of King George III. Ruler of the British Empire from 1760 to 1820, he presided over a considerable time span marked by great achievements and questionable decisions alike. Britain’s navy had proven itself as the undisputed world leader, defeating Napoleonic France and strengthening King George’s influence across the world. On the other hand, mismanagement of the American colonies led to Britain’s establishment of Australia as a penal colony, also controversial, was also conducted during his reign. These events left somewhat of a shadow over the legacy of King George III, “The King Who Lost America.” Subtle and not-so-subtle indications of Parliament’s hesitancy with King George’s rule stemmed from his periodic bouts of madness – bouts that while well documented would not receive a diagnosis for nearly 200 years. While evidence suggests minor episodes began much earlier, it was in October of 1788 that King George experienced his most prolonged bout of intense, totally debilitating madness, leaving England largely without a ruler until February of 1789 – a period often now referred to as The Regency Crisis. Royal physicians Dr. Richard Warren and Sir George Baker meticulously recorded symptoms of tachycardia, fever, periodic jaundice or bloodshot eyes, abdominal colic, constipation, lower leg cramps, pain, and weakness. They also noted bullous eruptions along the arms, hoarseness, and port-wine colored urine, as well as a variety of psychiatric manifestations including bouts of vivid multi-sensory hallucinations, delusions, and rambling which often degenerated into incoherent strings of obscenities.

Initially assumed to be a chiefly psychiatric disease, intriguing reports by royal attendants of urine that “leaves a pale blue ring upon the glass near the upper surface” left historians and physicians alike looking for a better answer. In the 1960’s Ida Macalpine and Richard Hunter first proposed that King George III was afflicted with acute intermittent porphyria (AIP), and with the permission of the royal family collected urine samples from his descendants, many of whom displayed elevated porphyrin levels. The subsequent discussion they sparked is perhaps unmatched in the field of medical history, and the mystery has spawned countless books and even an Oscar winning feature film. More recent proposals have integrated the observation of vesicular lesions to suggest instead a diagnosis of variegate porphyria (VP), though VP does not as commonly present with psychiatric manifestations, and rarely ever has it produced symptomology as severe as observed
in King George III.\textsuperscript{7} As this topic remains controversial, it is the intent of this article to address both AIP and VP.

**Epidemiology and Pathogenesis**

AIP results from an autosomal dominant mutation in the Porphobilinogen (PBG) deaminase gene.\textsuperscript{8} While mutation rates for this gene are relatively high, and more than 400 mutants have been identified, gene penetrance is low resulting in a disease prevalence of 1-2 per 100,000.\textsuperscript{9} VP, resulting from an autosomal dominant mutation in protoporphyrinogen oxidase (PPOX)\textsuperscript{8}, is just as heterogeneous in its mutations, and while one subtype occurs at a frequency of 1 per 300 in South Africa, global frequency is considerably lower. Furthermore, incidence of subtypes displaying associated psychiatric disease is rarer still leaving estimates as simply “less than AIP”.\textsuperscript{10}

Both genes are involved in the biochemical cascade required for the synthesis of protoporphyrin, the integral iron-bound component of hemoglobin. Defects in either of these two genes results in accumulation of both PBG and delta-aminolaevulinic acid (ALA).\textsuperscript{9} Interestingly, both of these compounds are colourless in the isolated state but develop a yellow, red, or purple pigment when left to react non-enzymatically in the urine.\textsuperscript{4}

Under normal circumstances the accumulation of biosynthetic intermediates is insufficient to produce symptoms of porphyria. However, under conditions of hematologic stress, most notably infection, blood loss, or Cytochrome P450 induction resulting from smoking, excess alcohol intake, fasting, fever, or pharmacologic interactions, porphyrin precursors accumulate to dangerous levels.\textsuperscript{9} While both ALA and PBG are implicated in triggering the neuropsychiatric aspects of porphyria, research has indicated that it is predominantly ALA that is responsible, by competitively inhibiting normal GABA receptor binding.\textsuperscript{9}

It has also been proposed that the extreme symptoms experienced by King George III may have been magnified by accidental, or perhaps iatrogenic arsenic exposure.\textsuperscript{1} It is well established that arsenic in its trivalent state can disrupt a number of the enzymes responsible for hemoglobin synthesis. Analysis of hair samples from King George III found arsenic traces

<table>
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<th>Stage</th>
<th>Signs and Symptoms</th>
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| Early through late (Abdominal) | Severe colicky abdominal pain (often epigastric lasting days)  
Constipation  
Nausea and vomiting |
| Mid through late (Psychiatric)* | Depression common  
Mania  
Psychosis |
| Late only (Neurologic) | Areflexia common  
Motor weakness, usually in lower limb  
Diffuse pain, usually in upper limb  
Autonomic neuropathy (hypertension, postural hypotension, tachycardia are common)  
Delirium, coma, cortical blindness also reported |
| Skin** | Photosensitive lesions, bulla or furrowing (most severe in children)  
Lesions often friable  
Hypertrichosis  
Sclerodermoid changes |
Much debate exists as to whether these symptoms have a pathogenic mechanism in VP. Observation of the South African cohort, where roughly 1 in 300 people have the gene for VP, suggests not.

** Skin manifestations only present in VP.

throughout the length of each hair, suggesting chronic exposure to low dose arsenic. It has been proposed that this exposure may have resulted from contamination of his antimonial emetic tartar, which at one point he was receiving at a rate of 120mg q6h. Treatments involving elemental compounds were quite popular at the time, and Dr. John Willis, head of Dunston House, London’s premier asylum of the time, was quite found of arsenic therapies. However, direct therapy using arsenic is not recorded in the logs of King George’s physicians.¹

The observation of a bluish layer precipitating to the surface of collected urine has also recently been explained.⁴ It has been observed that prolonged constipation can affect levels of bacterial sulphatase in the gastrointestinal tract, and in the presence of excess tryptophan, can lead to excessive production of indoxyl sulphate (indican). This substance is then processed in the liver and excreted via the kidneys. Barely soluble, it falls out of solution as urine temperature drops outside of the body. While this mechanism is largely believed, what is not understood is why this phenomenon is observed with greater frequency in patients suffering from an acute episode of porphyria.⁴

Diagnosis
Diagnosis relies on a high index of suspicion given the signs and symptoms of both AIP and VP (see Table 1).⁷,¹¹ It should be noted that symptom groups generally progress as overlapping groups, with initial manifestation limited to the abdomen, followed by psychiatric symptoms, and finally peripheral neuropathy. Ultimately, early morning or 24-hour urine collection should be conducted, ideally during an acute attack of the disease, and assessed for ALA and PBG accumulation.⁸ While levels will be substantially elevated during an acute attack, levels of both ALA and PBG, particularly PBG, remain elevated, often for years following the last acute attack.¹¹

Urine levels of ALA and PBG may be misleading if urine samples are left too long before analysis, particularly if exposed to light, or if collected from a patient with chronic renal failure. In this circumstance measuring direct ALA and PBG serum levels is indicated.⁷ Measurement of protoporphyrin and coproporphyrin in the stool may also assist in these circumstances, but is of low sensitivity.⁵ Recently, experts have also suggested that directly assessing PBG deaminase activity may be warranted as it unequivocally detects the defect associated with AIP.⁹

Differential
The differential diagnosis of acute porphyria is potentially enormous, thus diagnosis rests on successful identification of hemoglobin precursors in the urine, blood, or stool. The abdominal symptoms present in AIP are similar to many acute GI disorders.⁷⁻⁹,¹¹ Neuropsychiatric manifestations are most closely approximated by heavy metal poisoning. The skin lesions observed in cases of VP share similarities with a number of dermatological conditions, the most important to rule out include drug-induced photosensitivity reactions and porphyria cutanea tarda.⁷,⁹

Management
Successful management of acute attacks of porphyria rest on decreasing heme synthesis, in turn decreasing production and accumulation of heme precursors.⁹ Administration of high-dose glucose has been observed moderately curtail heme synthesis, if given in doses of at least 400g per day.¹¹ More severe attacks have been well managed with the use of hematin, a heme derivative, at a dosing of 4mg/kg/day for at least 4 days.¹¹

Just as important as treating acute attacks, prevention of further attacks is a critical aspect of management, and one that is complicated by significant pharmacologic interactions. Well over 200 drugs have been found to exhibit properties that may predispose an individual to more...
frequent bouts of porphyria. The classes felt to be most harmful include androgens, estrogens, progesterones, barbiturates, sulfonamides, hydantoins, griseofulvin, as well as ethanol. Due to the sheer volume of potential interactions, it is important to consult up to date, comprehensive lists when treating patients with AIP or any other porphyria.

Appropriate management must also include education and screening of family members. In asymptomatic individuals an assay for erythrocyte PGB deaminase has been found to be most sensitive in families with AIP. Similarly, assays for protoporphyrinogen oxidase have been used in assessing families with VP.

Conclusion

The acute porphyria diseases, despite being exceeding rare have captured a large portion of medical historians’ attention. In fact, it was King George and his regency crisis that many cite as one of the first and finest examples of ‘historical diagnosis’ to be discussed in the literature. Since the early papers on this topic a number of other historical figures have also been suggested to suffer from acute intermittent porphyria. As one would expect, many other British Royalty of King George’s bloodline have been afflicted, including Queen Anne, King James I, Queen Mary I of Scotland, and Frederic the Great of Germany. Other notable individuals often suggested to have had porphyria include Vincent van Gogh and King Nebuchadnezzar of Babylon.

References